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Diagnostic and Therapeutic Dilemmas of Cervical Ectopic Pregnancy

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Importance: Cervical pregnancy is a rare variety of ectopic pregnancy. The etiology is obscure. Its diagnosis may be difficult, and its management has enormously changed during the last 10 years. Unfortunately, the most effective, fertility-sparing treatment is still unclear until now.

Objectives: The aim of this study was to explore the safety and efficacy of different treatment modalities of cervical pregnancy.

Evidence Acquisition: A comprehensive systematic review of the literature was performed using the electronic databases MEDLINE and PubMed, using key words *cervical*, *ectopic*, and *pregnancy*, between January 2005 and June 2013. We included all case reports and case series reporting on cervical ectopic pregnancy.

Results: A total of 252 cases of cervical ectopic pregnancy were analyzed. Eighty-eight cases (34.9%) had medical treatment, 69 cases (27.5%) had surgical treatment, and 95 cases (37.6%) had combined medical and surgical treatment. Various conservative treatment regimens have been introduced to preserve fertility in young women, with methotrexate being one of the most widely used and effective drugs.

Conclusions and Relevance: A high index of suspicion, combined with meticulous review of clinical and radiological findings, is essential to make an accurate diagnosis of cervical pregnancy. The success of conservative treatment depends mainly on early diagnosis. Such cases would be best managed at specialist tertiary referral centers and preferably, where available, Early Pregnancy Assessment Units, whether medical, surgical, or combined treatment modalities were attempted.

Target Audience: Obstetricians, gynecologists, family physicians

Learning Objectives: After participating in this activity, physicians should be better able to identify the most likely predisposing factors for cervical ectopic pregnancy, appraise different modalities of treatment, and apply the selection criteria for conservative management of cervical ectopic pregnancy.

Cervical pregnancy is a rare type of ectopic pregnancy in which the pregnancy implants in the lining of the endocervical canal. It is the second rarest form after abdominal pregnancy. Its incidence is 1:16000 to 1:18000 of all pregnancies and 0.1% of all ectopic pregnancies.[1]

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Cervical pregnancy was first described by Sir Everard Home in 1817, who found an early ovum in the cervical canal during a postmortem examination after the case was misdiagnosed, and the patient died of severe hemorrhage.

Risks of Cervical Pregnancy

Cervical pregnancy is often associated with significant morbidity and devastating effects on future fertility. This can be due to the deep penetrative effect of the trophoblast through the cervical walls and into the uterine blood supply. Historically, 70% of the

reported cases required hysterectomy for massive blood loss.[2] The maternal mortality is reported to be 0% to 6%.[3,4]

The diagnosis and management of cervical pregnancy have considerably changed during the last 10 years. In view of the increasing incidence of the condition and the various therapeutic problems it poses, we are trying to explore its different methods of diagnosis and scrutinize the efficacy of its various treatment modalities.

Etiology

The causes of cervical pregnancy remain unknown. The rarity of the condition has prevented any retrospective study with adequate numbers to determine the potential risk factors. Several studies have shown a high incidence of prior dilation and curettage among women with cervical pregnancies,[5,6] especially when the curettage damaged the endometrial lining and prevented implantation of the fertilized ovum. Endometrial inflammation from the use of an intrauterine device and pelvic inflammatory disease could also be a contributing factor.[7]

Pure mechanical factors such as intrauterine myomas, uterine malformations, and alterations in the uterine tone have also been proposed. Normally, the uterine tone is increased in the body and reduced in the cervix throughout the proliferative phase and vice versa during the secretory phase. If the conditions of tone from the first phase persist during the second phase, this may lead to the ovum being released from the corporeal cavity of the uterus while it is still capable of nidation.[8]

Several case reports have also suggested an increased incidence of cervical pregnancies in women undergoing in vitro fertilization.[9,10] However, the strength of such associations with cervical pregnancy is generally very imprecise (Table 1). On the other hand, the incidence might have seemed to be increased owing to the early diagnosis by endovaginal ultrasound examination of cervical pregnancies, some of which would have aborted spontaneously.

TABLE 1
Predisposing Factors of Cervical Ectopic Pregnancy

Previous instrumentation of the endocervical canal	In vitro fertilization
Anatomic anomalies (myomas, synechiae)	Diethylstilbestrol exposure
Previous cesarean delivery	Intrauterine device use
Chromosomal abnormalities in the embryo	Variations in uterine tone
Previous cervical or uterine surgery	Pelvic inflammatory diseases

Pathology

Pregnancy implantation in the cervix lacks the protective decidual plate seen in the corpus, which acts as a blockage to the invading chorionic villi. Cervical tissue is, therefore, destroyed by the chorionic villi eroding the surrounding structures, including the large vessels in the path of expansion. Consequently, placental implantation in a true cervical pregnancy is essentially one of placenta accreta lacking the cleavage plane.[11] Any cervical pregnancy that progresses beyond 12 weeks will transgress the internal os and will be classified as isthmicocervical rather than primary cervical pregnancy. According to Schneider and Dreizin,[12] such pregnancies are more dangerous than those entirely restricted to the cervix because trophoblasts are more likely to erode the uterine blood vessels.

Diagnostic Criteria

Before the advent of ultrasound, the diagnosis of cervical pregnancy was difficult and was often made after hysterectomy was done for uncontrollable bleeding. Ultrasonography, especially transvaginal sonography, and serial serum human chorionic gonadotropin (hCG) levels estimation permit early and accurate diagnosis of ectopic pregnancy. If the increase in serum hCG concentration after 48 hours is less than 63%, the chance of ectopic pregnancy is considerably high.

Pathologic Criteria

The pathologic criteria for diagnosis of cervical pregnancy were set forth by Rubin[13] in 1911 as follows:

(1) Cervical glands must be opposite the placental attachment.
(2) The placental attachment to the cervix must be intimate.
(3) The placenta must be situated, in whole or in part, either below the entrance of the uterine vessels or below the peritoneal reflection on the anterior and posterior surfaces of the uterus.
(4) Fetal elements must not be present in the corpus uteri.

Obviously, these criteria can be satisfied only if the whole uterus and cervix are available for pathologic study (postmortem or hysterectomy specimens).

Clinical Criteria

Painless vaginal bleeding is the most common presentation, with only one third of women presenting by massive hemorrhage. In 1959, Paalman and McElin[14] offered 5 clinical signs to establish the diagnosis as follows:

(1) Uterine bleeding without cramping pain after a period of amenorrhea.
(2) Softened and disproportionately enlarged cervix equal to or larger than the corporal portion of the uterus (an hourglass-shaped uterus).
(3) Products of conception entirely confined within, and firmly attached to, the endocervix.
(4) A snug internal os.
(5) A partially opened external os.

Sonographic Criteria

The combination of transvaginal and transabdominal ultrasonography using high-resolution transducers would establish a diagnosis in most of the cases in the first trimester. This is essential because only cases diagnosed before 12 weeks, that is, before the trophoblast has infiltrated too deeply into the cervical wall, are amenable to conservative treatment.

In 1978, Raskin[15] suggested 4 sonographic diagnostic criteria (Figs. 1 and 2) as follows:

(1) Enlargement of the cervix
(2) Uterine enlargement
(3) Diffuse amorphous intrauterine echoes
(4) Absence of intrauterine pregnancy

In 1996, Jurkovic et al[16] proposed 2 additional diagnostic criteria to distinguish cervical ectopic pregnancy from an aborting intrauterine pregnancy residing in the cervix as follows:

(5) The "sliding sign" detected on transvaginal ultrasound examination, when the gestational sac of an abortus slides against the endocervial canal after gentle pressure on the cervix with the vaginal probe. This sign would not be seen in an implanted cervical pregnancy.
(6) The demonstration of peritrophoblastic blood flow to the conceptus by color flow Doppler ultrasonography. The nonviable sac, transiently passing through the cervix, will not have such blood flow and will show a positive sliding sign, and the closed internal os will differentiate it from an isthmicocervical pregnancy.

FIG. 1. Detailed yolk sac in the cervix with the embryo inside. Reprinted with permission from TheFetus.net.

FIG. 2. Sagittal transabdominal view showing dilated cervical canal due to the cervical pregnancy. Reprinted with permission from TheFetus.net.

Three-dimensional transvaginal ultrasound may also be useful in obese women or in cases with retroverted uterus, allowing better analysis of the endometrial cavity on coronal planes.[17]

A sonographic impression of cervical pregnancy is correct in 87.5% of cases. However, when the ultrasound is inconclusive, magnetic resonance imaging may be helpful in unusual or complicated cases.[18]

Management

Whereas great advances have been made in the diagnosis and treatment of most extrauterine pregnancies, cervical pregnancy remains a challenge. Early detection is the key factor for conservative management. Negative results are less frequently published, which disturbs the evaluation of the outcome results. Cervical pregnancies before 12 weeks, without fetal cardiac activity and with low serum hCG levels, seem more amenable to conservative treatment.

General principles in conservative management should include (1) minimizing the risk for hemorrhage, (2) eliminating gestational cervical products, and (3) preserving the uterus and/or fertility. Table 2 shows

the different medical, surgical, and combined treatment modalities of cervical ectopic pregnancy.

Medical Treatment

Primary medical treatment of early cervical pregnancy carries better prognosis than surgery and could prevent the need for hysterectomy in more than 91% of cases.[19,20] Current literature review showed that the risk for major hemorrhage in the medical group was 11% with a 3% hysterectomy rate, compared with the surgical group, in which the hemorrhagic risk was 35% with a 15% hysterectomy rate. However, women should be thoroughly counseled and advised about the procedure risks and the difficulty of prediction of posttreatment complications.

The Role of Methotrexate

Methotrexate treatment of cervical pregnancy was first performed by Farabow et al[21] in 1983. Methotrexate is a chemotherapeutic agent that has the ability to inhibit growth of the trophoblast by inhibiting DNA synthesis and cell division. However, it is contraindicated in active renal or hepatic disease or in the presence of leukopenia or thrombocytopenia.

The dose regimens of systemic methotrexate varied considerably. Single dose (50 mg/m^2 intramuscularly [IM]) with monitoring of serum hCG levels on days 4 and 7 was described. If the difference in serum hCG levels is 15% or greater, the test is repeated weekly until it becomes undetectable. If the difference is less than 15%, methotrexate dose should be repeated, and new day 1 is begun. Multiple-dose regimens can also be used (1 mg/kg on days 1, 3, 5, 7, and 9 IM), with or without 0.1 mg/kg of folinic acid rescue (leucovorin) on alternate days. No more than 5 doses of methotrexate are to be given without a gap of 1 week. In 2009, an alternative high-dose regimen of methotrexate was suggested by Song et al[22] in the form of a single course of 100 mg/m^2 plus a dose of 200 mg/m^2 in 500 mL of normal saline solution via intravenous injection with a 0.1 mg/kg of folinic acid rescue.

Methotrexate can also be used intracervically or intraamniotically in a dose of 50 mg/m^2. However, there is a strong possibility of active bleeding after local injection, caused by rupture of the intra-amniotic membrane. Unfortunately, the present data are too limited and inconsistent to compare the efficacy of different regimens.

The resolution time of cervical pregnancy after chemotherapy, as determined by serum hCG levels, varied from 2 to 5 weeks and, by sonographic appearance of the cervix, varied from 2 to 12 weeks. A possible problem with methotrexate therapy is the inability to predict the occurrence of massive bleeding, after trophoblast shedding, from the uninvoluted and atonic cervix.

Current literature review showed that 49% of viable cervical pregnancies have required an additional operative procedure to eradicate the aberrant trophoblastic tissue.

In general, the prognostic factors for an unsatisfactory primary methotrexate treatment of cervical pregnancy include the presence of serum hCG levels of 10,000 mIU/mL or greater, gestational age of 9 weeks or later, presence of fetal heartbeat, or fetal crown-rump length of greater than 10 mm.

TABLE 2
Different Treatment Modalities of Cervical Ectopic Pregnancy

Conservative
Medical
Methotrexate: local, systemic, intra-arterial, intra-amniotic, or intra-cervical
KCl: local, intra-amniotic, or intracardiac
Local vasopressin injection
Local or systemic prostaglandin
Local hyperosmolar glucose 33% or hypertonic sodium chloride
Systemic mifepristone
Intrauterine irrigation with 3.5% H_2O_2
Surgical
Local sac aspiration using plastic cannula
Suction evacuation
Curettage with or without dilation
Hysteroscopic endocervical resection evacuation with or without coagulation
Cervical cerclage (McDonald, Shirodkar)
Local hemostatic sutures
Angiographic UAE: unilateral or bilateral
Vaginal cervicotomy (Matracaru operation)
Transvaginal ligation of the cervicovaginal branches of the uterine arteries
Bilateral uterine or internal iliac arteries ligation
Tamponade
Foley catheter (size 26 with 30-mL balloon)
Sengstaken-Blakemore tube
Cervical/vaginal packing
Combined medical and surgical
Radical
Cervical amputation
TAH

The Role of Potassium Chloride

Local injection of potassium chloride (KCl) (3–5 mL of 2 mEq/mL) under transvaginal ultrasound guidance is an alternative to methotrexate treatment. This method has been used as a primary therapy and in combination with systemic chemotherapy or after failed systemic methotrexate treatment, with 90% success

rate.[2] Thus, KCl injection can be a viable option in the treatment of heterotopic cervical pregnancy without the need for local or systemic chemotherapy. However, there is still a possibility of major hemorrhage or infection of the implantation site, and further procedures may be required.

The Role of Prostaglandins

Use of prostaglandins in cervical pregnancies was reported by few authors. Dall et al[23] reported its use, both systemically and intra-amniotically, in a 9-week cervical pregnancy, but despite simultaneous curettage, intractable hemorrhage necessitated an emergency hysterectomy. Spitzer et al[24] subsequently described 3 cases of first-trimester cervical pregnancy that were successfully treated with curettage and local prostaglandin instillation (12.5–25 μg of sulprostone).

The Role of Hydrogen Peroxide

Hysteroscopic management of cervical pregnancy with intrauterine irrigation with 3.5% hydrogen peroxide (H_2O_2) has been performed on 10 cases by Kim et al[25] and was found to be a safe and effective alternative treatment. Hydrogen peroxide solution releases a large amount of free oxygen via catalysis, which is very abundant in embryos and the yolk sac and induces cell death because of oxygen toxicity.

The Role of Mifepristone

Mifepristone acts as a competitive antagonist to progesterone at the receptor level. It indirectly induces decidual breakdown, leading to trophoblast detachment and decreased syncytiotrophoblast production of hCG, which, in turn, causes decreased production of progesterone by the corpus luteum.[26] The combination of mifepristine with methotrexate is claimed to prevent the development of embryos and speed up embryonic death, which, in turn, would shorten the treatment time. The dose of mifepristone used was usually 25 to 75 mg twice daily for 3 to 5 days orally.

The Role of Ecbolics

Intracervical or systemic injections of syntocinon and/or ergometrine have no role in the management of cervical pregnancy because the uterine cervix consists mainly of fibrous connective tissue with only 10% smooth muscle. However, they may have a role in cases of cervicoisthmic implantation because the isthmus area has 50% to 60% muscular connective elements.[27]

Surgical Treatment

This can be used either alone or in combination with medical treatment.

Dilation and Curettage (Surgical Evacuation)

Dilation and curettage alone carries a 40% risk for hysterectomy.[16] Attempts to evacuate the uterus digitally or instrumentally will produce violent hemorrhage, necessitating hysterectomy in most cases. If tamponade provides successful hemostasis primarily, severe secondary hemorrhage necessitating hysterectomy may, nevertheless, occur up to 6 weeks later. The outcome is significantly better when combined with other medical or surgical methods to control blood loss and to prevent residual gestational tissue from active regrowth with the establishment of collateral circulation after uterine artery embolization (UAE).

Angiographic Embolization

Securing the blood supply to cervical pregnancy by angiographic UAE was first introduced in 1990 by Lobel et al.[28] Gelfoam particles (Upjohn) or polyvinyl alcohol (Boston Scientific) provides temporary occlusion of the vessel for 2 to 6 weeks. Its advantages over other treatment modalities include shorter hospital stay, fewer laboratory follow-ups, fewer outpatient checkups, and prevention of hemorrhage. However, women should be appropriately counseled about the possible impairment of fertility, loss of ovarian reserve, and the occurrence of obstetric complications in future pregnancies.

The risk factors of recurrent vaginal bleeding after UAE are fetal cardiac activity before therapy, persistent high hCG level, and recurrent flow signal around the intracervical gestational sac. In 2004, Kung et al[29] used an alternative combination of laparoscopically assisted uterine artery ligation followed by hysteroscopic endocervical resection to successfully treat 6 cervical pregnancies. Uterine artery embolization between angiographic and (UAE).

Cervical Cerclage

Scott et al[30] was the first to report the successful application of Shirodkar cervical cerclage in cervical pregnancy. In 2002, Mashiach et al[31] described the successful management of 4 cervical pregnancies using a Shirodkar suture, and in one of these cases, a concurrent uterine pregnancy progressed to term.

Total Abdominal Hysterectomy

Total abdominal hysterectomy (TAH) is the treatment of choice for patients with cervical pregnancies

TABLE 3
Review of Medical Treatment Only Since January 2005

Study	N	GA, wk	Serum hCG, mIU/mL	Procedure	Comments
De Greef et al[32] (2005)	1	6	35,870	Multiple-dose MTX + mifepristone	
Doekhie et al[33] (2005)	1	6.3	71,000	USS-guided sac aspiration + local MTX	
Yildizhan[34] (2005)	1	6	NA	Single-dose MTX + local MTX	
Api et al[35] (2006)	1	6	19,000	Multiple-dose MTX	
Grimbizis et al[36] (2006)	1	8	1440	Multiple-dose MTX + local MTX	
Jeng et al[37] (2006)	1	14	32,085	USS-guided intra-amniotic MTX + intracardiac KCl	
Ruano et al[38] (2006)	1	14	884	Multiple-dose MTX	
Emmi et al[39] (2007)	1	6	16,113	Multiple-dose MTX	
Ferrara et al[40] (2007)	1	7	10,012	Single-dose MTX + USS-guided intra-amniotic MTX + KCl	
Jeng et al[41] (2007)	38	5.4–14	5608–103,256	USS-guided intra-amniotic MTX	Two cases had additional IM single-dose MTX because of nondeclined serum hCG titer
				In 22 cases with positive fetal life, additional intracardiac KCl was given	Three cases had Foley catheter tamponade and additional IM single-dose MTX because of severe vaginal bleeding
Suzuki et al[42] (2007)	1	6	NA	USS-guided sac aspiration + instillation of hyperosmolar glucose	Twin intrauterine pregnancy delivered (34/40) by C/D because of PROM and massive vaginal bleeding (heterotopic pregnancy)
Vela and Tulandi[43] (2007)	2	8	4029	Single-dose MTX	
		8	380	Two-dose MTX	
Ben Hamouda et al[44] (2008)	1	7	NA	Two-dose MTX	
Cerveira et al[45] (2008)	1	7	NA	Single-dose MTX + USS-guided intra-amniotic MTX	
Cipullo et al[46] (2008)	1	7	5300	Multiple-dose MTX	Echoscope-guided intracardiac KCl 1 wk later
Giarenis et al[47] (2008)	1	6	3098	Vaginal packing+ multiple-dose MTX	
Sherer et al[17] (2008)	1	6	5859	Multiple-dose MTX	Second course of multiple-dose MTX 1 wk later
Majumdar et al[48] (2009)	1	8	NA	USS-guided intracardiac KCl injection	IUP delivered (31/40) by C/D because of absent EDF of UA (heterotopic pregnancy)
Pandher and Shehgal[49] (2009)	1	10	6716	Single-dose MTX	

Song et al[22] (2009)	24	14.3	4800	High-dose MTX regimen	Failed, had TAH
		5.5	24,100	High-dose MTX regimen	Failed, had TAH
		6.4	1736	Multiple-dose MTX	Failed, had TAH
		5.4	NA	Multiple-dose MTX	
		6.1	9100	Single-dose MTX	
		5.6	6300	Multiple-dose MTX	
		5.1	15,614	Multiple-dose MTX	
		6.6	6064	Multiple-dose MTX	
		5	580	Single-dose MTX	
		6.4	65,000	High-dose MTX regimen + multiple-dose MTX	
		6.5	41,750	High-dose MTX regimen + multiple-dose MTX	
		5.6	3285	High-dose MTX regimen	
		5.3	13,400	High-dose MTX regimen	Had 5 repeated courses of high-dose MTX regimen
		5.3	5000	Multiple-dose MTX	Had 2 repeated courses of high-dose MTX regimen
		5.5	10,424	High-dose MTX regimen	Had second course of high-dose MTX regimen
		5.1	5100	High-dose MTX regimen	Had second course of high-dose MTX regimen
		6.1	19,000	High-dose MTX regimen	
		5.6	47,100	High-dose MTX regimen + intra-amniotic KCl	Had second course of high-dose MTX regimen
		6.2	5800	High-dose MTX regimen + intra-amniotic KCl	
		6	15,800	High-dose MTX regimen	Had second course of high-dose MTX regimen
		6.2	4940	High-dose MTX regimen	
		8	22,234	High-dose MTX regimen	
		6.3	5600	High-dose MTX regimen	
		5.6	2700	High-dose MTX regimen	
Moon et al[50] (2010)	1	6.4	24,076	Multiple-dose MTX + USS-guided sac aspiration + local MTX	
Taylor et al[51] (2011)	3	7	21,041	Single-dose MTX	
		6	2776	Single-dose MTX	
		7	29,682	Multiple-dose MTX	
Deka et al[52] (2012)	1	11	NA	Local KCl + local MTX	IUP delivered (36/40) by C/D because of impending eclampsia (heterotopic pregnancy)
Weibel et al[53] (2012)	2	5.6	12,306	Multiple-dose MTX	
		7.4	9988	Multiple-dose MTX	

C/D, cesarean delivery; EDF, end diastolic flow; GA, gestational age; IUP, intrauterine pregnancy; MTX, methotrexate; NA, not available; PROM, premature rupture of membranes; UA, umbilical artery; USS, ultrasound.

TABLE 4
Review of Surgical Treatment Only Since January 2005

Study	N	GA, wk	Serum hCG, mIU/mL	Procedure	Comments
Trambert et al[54] (2005)	1	9	NA	UAE	
Ujvari et al[55] (2006)	1	6	NA	USS-guided sac aspiration	Twin IUP delivered (29/40) by C/D because of placental abruption (heterotopic pregnancy)
De La Vega et al[56] (2007)	1	8	>50,000	Intracervical infiltration of carboprost + cervical cerclage + suction evacuation + Foley catheter tamponade	Foley catheter was removed on day 2; and the cerclage, on day 7
Hu et al[57] (2007)	1	9.2	NA	Exploratory laparotomy + abdominal resection of the sac + Foley catheter tamponade	
Martinelli et al[58] (2007)	2	11	NA	UAE + curettage	
		9	NA	UAE + curettage	TAH due to severe infection 2 wk later
Vela and Tulandi[43] (2007)	7	7	NA	Curettage	Failed, had TAH
		16	1100	TAH	
		14	NA	Ligation of cervical branches of uterine vessels + curettage + vaginal packing	
		12	NA	Curettage	Failed, had TAH
		8	17,000	Curettage + cervical suturing + Foley catheter tamponade + vaginal packing	Failed, had TAH
		10	432	Curettage + vaginal packing	
		10	13,200	Curettage + cervical suturing + Foley catheter tamponade	
Yang et al[59] (2007)	1	8	27,529	UAE + USS-guided curettage	Had repeat UAE 2 d later because of severe vaginal bleeding. Had temporary intraoperative balloon occlusion of bilateral CIA + hysteroscopic endocervical resection of gestational sac + Foley catheter tamponade 10 d later
Aytan et al[60] (2008)	1	NA	8320	Surgical evacuation	Cervical partial hydatidiform molar pregnancy
Biswas et al[61] (2008)	1	21	NA	Exploratory laparotomy + bilateral IIA ligation + abdominal hysterotomy	Failed, had TAH
Cipullo et al[46] (2008)	1	5	1200	Ligation of cervical branches of uterine vessels + curettage + Foley catheter tamponade	Failed, had TAH
Fruscalzo et al[62] (2008)	1	16	NA	Curettage + cervical suturing	Spontaneous miscarriage of IUP few hours later (heterotopic pregnancy)
Hanstede et al[63] (2008)	1	18.5	NA	Surgical TOP	Failed, had TAH
Nakao et al[64] (2008)	2	6	3951	UAE + curettage	
		7	25,700	UAE + curettage	

(Continued on next page)

TABLE 4. *(Continued)*

Study	N	GA, wk	Serum hCG, mIU/mL	Procedure	Comments
Hoshino et al[65] (2009)	1	9	NA	Surgical evacuation	IUP delivered (38/40) by C/D because of previous abdominal myomectomy (heterotopic pregnancy)
Kim et al[66] (2009)	1	8	NA	USS-guided sac aspiration + Foley catheter tamponade	IUP delivered (37/40) by C/D because of breech presentation (heterotopic pregnancy)
Pandher and Shehgal[49] (2009)	2	13	NA	Surgical evacuation	Failed, both women had laparotomy, bilateral uterine artery ligation, hysterotomy, and uterine packing
		14	NA	Surgical evacuation	
Shah et al[67] (2009)	1	7	NA	USS-guided sac aspiration	IUP delivered (37/40) by C/D, after preoperative placement of bilateral hypogastric artery occlusion balloons, because of previous abdominal myomectomy (heterotopic pregnancy)
Song et al[22] (2009)	20	7	NA	Surgical evacuation	Failed, had TAH
		6.2	NA	Surgical evacuation + packing	
		6.2	9000	Surgical evacuation	
		6.4	11,100	Surgical evacuation	
		7.4	1570	TAH	
		7.2	28,200	Surgical evacuation	
		6.5	NA	Surgical evacuation + Foley catheter tamponade	
		11.2	NA	Surgical evacuation + Foley catheter tamponade	
		8	2970	TAH	
		6.5	5800	Surgical evacuation	
		8	NA	Surgical evacuation	
		5.5	39,400	Surgical evacuation	
		5.3	7401	TAH	
		7.1	3870	Surgical evacuation	
		6.1	19,900	Surgical evacuation	
		6.3	1615	Surgical evacuation	
		7.6	68,000	Surgical evacuation	Failed, had TAH
		5.6	NA	Surgical evacuation	
		5.4	12,714	Surgical evacuation	
		7	44,601	Surgical evacuation	
Yu et al[68] (2009)	1	9	NA	UAE + surgical evacuation	
Bianchi et al[69] (2011)	1	7	100,685	Ligation of cervicovaginal branches of uterine vessels + USS-guided curettage + cervical cerclage + cervical packing	
Faschingbauer et al[70] (2011)	1	9	NA	Cervical cerclage + USS-guided curettage	IUP delivered (39/40) by V/D (heterotopic pregnancy)
Mohebbi et al[71] (2011)	1	6.1	10,649	Surgical evacuation	

(Continued on next page)

TABLE 4. *(Continued)*

Study	N	GA, wk	Serum hCG, mIU/mL	Procedure	Comments
Wang et al[72] (2011)	12	5.5	8395	UAE	
		8.1	NA	UAE	
		8.4	32,378	UAE	
		7.5	56,434	UAE	
		7.4	30,312	UAE + curettage	
		6.2	13,425	UAE	
		8.4	>10,000	UAE	
		7.1	252	UAE	
		6.6	8409	UAE	
		9.2	743	UAE + curettage	
		5.2	17,982	UAE (heterotopic pregnancy)	Spontaneous miscarriage of both pregnancies 3 d later
		7.1	9574	UAE	
Kim et al[73] (2012)	1	5.2	NA	USS-guided surgical evacuation	IUP delivered (40/40) by C/D because of failure to progress (heterotopic pregnancy)
Mayer et al[74] (2012)	1	8	NA	USS- and hysteroscopic-guided sac aspiration	IUP delivered (37/40) by C/D because of fetal bradycardia (heterotopic pregnancy)
Scutiero et al[75] (2013)	5	6	18,726	UAE + hysteroscopic endocervical resection	
		9	26,726	UAE + hysteroscopic endocervical resection	
		6	42,141	UAE + hysteroscopic endocervical resection	
		7	15,482	UAE + hysteroscopic endocervical resection	
		8	74,684	UAE + hysteroscopic endocervical resection	

C/D, cesarean delivery; CIA, common iliac artery; GA, gestational age; IIA, internal iliac artery; IUP, intrauterine pregnancy; NA, not available; TOP, termination of pregnancy; USS, ultrasound; V/D, vaginal delivery.

diagnosed during the second trimester, with unstable vital signs and excessive vaginal bleeding, with associated uterine pathology, who are Jehovah's witnesses, and who have completed their families. However, there will still be an increased risk for urinary tract injury because of the enlarged barrel-shaped cervix.

We systematically reviewed the English-language literature on cervical pregnancy using the electronic database of PubMed and MEDLINE between January 2005 and June 2013. The search titles were subject words *cervical*, *ectopic*, and *pregnancy*. Our review resulted in 69 relevant articles of 252 cases (19 case series and 50 case reports) of cervical ectopic pregnancy in the studied period. Eighty-eight cases (34.9%) had medical treatment (Table 3), 69 cases (27.5%) had surgical treatment (Table 4), and 95 cases (37.6%) had combined medical and surgical treatment (Table 5). In view of the lack of uniformity and consistency in the data and in the management of such cases, we have not made any calculations as to statistical significance. This study involved published data and thus did not require ethics approval.

Heterotopic Pregnancy

A cervical heterotopic pregnancy provides a very unique position for which high maternal risks are implied. Termination of cervical pregnancy should be done using minimally invasive conservative procedure without disturbing the intrauterine gestational sac. Eleven cases of heterotopic pregnancy with subsequent live births were reported in the current study. Four women delivered at term, and 7 women had preterm delivery because of maternal or fetal complications. All the women, except 1, underwent cesarean delivery.

Reproductive Performance After Cervical Pregnancy

The impact of cervical pregnancy on future fertility is largely unknown because of the rarity of the condition and the infrequency with which women were

TABLE 5
Review of Combined Medical and Surgical Treatment Since January 2005

Study	N	GA, wk	Serum hCG, mIU/mL	Procedure	Comments
Hassiakos et al[76] (2005)	6	5–8	4100–10,500	USS-guided local MTX + D&C	Same treatment for all women
Mesogitis et al[77] (2005)	9	6	6500	USS-guided sac aspiration + local MTX + curettage	
		7.1	7600	USS-guided sac aspiration + local MTX + curettage	
		6.5	7900	USS-guided sac aspiration + local MTX + curettage	
		6.2	7250	USS-guided sac aspiration + local MTX + curettage	
		7.3	10,355	USS-guided sac aspiration + local MTX + curettage	
		6.6	11,220	USS-guided sac aspiration + local MTX + curettage	
		7.5	31,105	USS-guided sac aspiration + local MTX + curettage	
		6.5	7455	USS-guided sac aspiration + local MTX + curettage	
		6.3	7210	USS-guided sac aspiration + local MTX + curettage	
Trambert et al[54] (2005)	7	7	NA	UAE + single-dose MTX + D&C	
		8	NA	UAE + single-dose MTX	Had second course of single-dose MTX
		5	NA	UAE + local MTX + D&C	
		6.5	NA	UAE + single-dose MTX	Had repeat UAE and second course of single-dose MTX
		6	NA	UAE + local MTX	
		5	NA	UAE + single-dose MTX	
		8	NA	UAE + single-dose MTX	Had second course of single-dose MTX
Vilos et al[78] (2005)	1	10.5	97,000	Single-dose MTX + UAE + hysteroscopic resection + suction evacuation	
Grimbizis et al[36] (2006)	4	13	18,545	Multiple-dose MTX + local MTX + curettage + tamponade	Had curettage twice
		10	36,800	Multiple-dose MTX + local MTX + curettage + tamponade	
		7	9223	Multiple-dose MTX + local MTX + curettage + tamponade	
		6	4712	Multiple-dose MTX + local MTX + curettage + tamponade	
Matteo et al[79] (2006)	1	7	NA	Single-dose MTX + hysteroscopic endocervical resection	
Starita et al[80] (2006)	1	9	NA	MTX + ligation of cervical branches of uterine vessels + hysterosuction + Foley catheter tamponade	Failed, had TAH
Mancuso et al[81] (2007)	2	8.1	NA	Multiple-dose MTX + ligation of cervical branches of uterine vessels + curettage	Same management for both women
		8	2880		
Martinelli et al[58] (2007)	1	12	NA	Multiple-dose MTX + UAE + curettage	
Nadisauskiene et al[82] (2007)	1	7	31,930	Multiple-dose MTX	Had UAE + curettage + Foley catheter tamponade 4 d later
Nitke et al[83] (2007)	1	7	61,596	Intra-arterial MTX +UAE	TOP of heterotopic pregnancy

(Continued on next page)

TABLE 5. *(Continued)*

Study	N	GA, wk	Serum hCG, mIU/mL	Procedure	Comments
Prorocic et al[84] (2007)	1	6	74,572	Ligation of cervical branches of uterine vessels + USS-guided sac aspiration + instillation of hypertonic sodium chloride	Twin IUP of unknown outcome (heterotopic pregnancy)
Sabadell et al[85] (2007)	1	NA	44,152	Single-dose MTX	Had UAE 6 d later
Sanu et al[86] (2007)	1	15	NA	Mifepristone + systemic and local MTX + USS- and laparoscopic-guided surgical evacuation + Sengstaken-Blakemore tube tamponade + MacDonald cervical cerclage	
Tinelli et al[87] (2007)	1	7	65,900	Single-dose MTX	Had ligation of cervical branches of uterine vessels + USS-guided curettage + cervical packing 3 d later
Vela and Tulandi[43] (2007)	3	6.5	22,324	Single-dose MTX + local KCl + curettage + ligation of cervical branches of uterine vessels	Failed, had TAH
		9.1	6107	Single-dose MTX + UAE	
		6.6	NA	Single-dose MTX + UAE	TOP of heterotopic pregnancy
Xu et al[88] (2007)	2	8.1	45,830	Multiple-dose MTX + UAE + mifepristone	Had repeat UAE + curettage 19 d later
		7.6	25,600	Single-dose MTX + mifepristone	Had UAE + curettage 16 d later
Cipullo et al[46] (2008)	3	7.3	8400	UAE + multiple-dose MTX	Had second course of multiple-dose MTX 2 wk later
		8.2	8000	UAE + multiple-dose MTX	
		7.1	6700	UAE + multiple-dose MTX	
Corticelli et al[89] (2008)	1	5.5	12,396	Multiple-dose MTX	Had curettage and Foley catheter tamponade 2 d later
Davis et al[90] (2008)	1	NA	4774	Ligation of cervical branches of uterine vessels + local vasopressin + curettage	
Kim et al[25] (2008)	10	4	4039	Intrauterine 3.5% H_2O_2 irrigation + hysteroscopic resection evacuation with or without electrocoagulation	Same management for all women
		5	12,447		
		6	16,546		
		5.6	19,870		
		6.2	25,139		
		5	5699		
		5	12,391		
		5.6	47,629		
		4	1561		
		6	11,321		
Lin et al[91] (2008)	1	7	14,988	Single-dose MTX	Had ligation of cervical branches of uterine vessels + intracervical vasopressin + hysteroscopic resection and coagulation 2 wk later

Song et al[22] (2009)	6	6.1	3480	Single-dose MTX + D&C	
		6	11,400	High-dose MTX regimen + D&C	Had second course of high-dose MTX regimen
		7	36,300	Multiple-dose MTX + D&C	
		6	14,300	High-dose MTX regimen + uterine artery ligation + D&C	
		5	4310	High-dose MTX regimen + uterine artery ligation	Had second course of high-dose MTX regimen
		9	196,000	High-dose MTX regimen + uterine artery ligation + D&C	Had 3 repeat courses of high-dose MTX regimen
Farhat et al[92] (2010)	1	11	NA	USS-guided intra-amniotic KCl + UAE + curettage	Cervical twin pregnancy
Hafner et al[93] (2010)	1	6	217,000	Foley catheter tamponade + cervical cerclage at level of external os + ligation of descending cervical branches of uterine vessels + multiple-dose MTX	Had TOP (heterotopic pregnancy) 3 d later
Xiaolin et al[94] (2010)	20	4–12	1206-37,710	Intra-arterial methotrexate infusion + UAE	Five cases had additional curettage (with persistent serum hCG > 10,000 mIU/mL after treatment)
Gowri et al[95] (2011)	1	11	6943	Curettage + Foley catheter tamponade + UAE + single-dose MTX	
Sanchez-Ferrer et al[96] (2011)	1	6.5	NA	Intra-arterial MTX + UAE	TOP of heterotopic pregnancy
Taylor et al[51] (2011)	1	7	29,682	Single-dose MTX + UAE + surgical evacuation	
Wang et al[72] (2011)	4	8.1	45,830	Single-dose MTX + UAE	Had UAE twice
		7.6	25,600	Single-dose MTX + UAE	
		8.4	1392	Single-dose MTX + mifepristone + UAE	
		10	1536	Single-dose MTX + UAE	
Uysal and Uysal[97] (2013)	1	7	NA	USS-guided intra-amniotic KCl + USS-guided sac aspiration + cervical cerclage + Foley catheter tamponade	Foley catheter and cerclage were removed 2 d later, IUP delivered (38/40) by C/D because of previous 2 C/Ds (heterotopic pregnancy)

C/D, cesarean delivery; D&C, dilation and curettage; GA, gestational age; IUP, intrauterine pregnancy; MTX, methotrexate; NA, not available; TOP, termination of pregnancy; USS, ultrasound.

observed after treatment. It is also unclear whether there is an increased risk for recurrence. Women, therefore, should be counseled about the risk for future ectopic pregnancies, second-trimester pregnancy losses, and the potential need for subsequent prophylactic cervical cerclage.

In a review of 120 published cases of cervical pregnancy, Ushakov et al[3] found 37 pregnancies identified after conservative management of cervical pregnancy, 34 intrauterine pregnancies, 2 tubal pregnancies, and 1 repeat cervical pregnancy. Current literature review found 38 pregnancies identified after conservative management of cervical pregnancy; all of them were intrauterine pregnancies; 6 women had first-trimester spontaneous miscarriage, with subsequent full-term pregnancy in 3 of them; 1 woman had surgical termination of pregnancy; 1 woman had preterm labor; 1 woman had intrauterine fetal death at 26 weeks; another one had 8 weeks of intrauterine pregnancy with unknown outcome; and 28 had successful pregnancy outcome at full term.

CONCLUSIONS

Cervical ectopic pregnancy remains a major challenge in the field of early pregnancy. In this study, we have summarized the various methods of diagnosis and evaluated the efficacy of its various treatment modalities. A high index of suspicion, combined with meticulous review of clinical and radiological findings, is essential to make an accurate diagnosis of cervical pregnancy. The success of conservative treatment depends mainly on early diagnosis. Such cases would be best managed at specialist tertiary referral centers and preferably, where available, Early Pregnancy Assessment Units, whether medical, surgical, or combined treatment modalities were attempted. An organized system of data collection such as registry of cervical pregnancies on Web sites of specialty institutes would probably be the best way to collect the accurate statistics for the condition and assess the effectiveness of various treatment modalities.

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